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(54) Title: PHARMACEUTICAL TABLET CAPABLE OF LIBERATING ONE OR MORE DRUGS AT DIFFERENT RELEASE RATES (57) Abstract Pharmaceutical tablet consisting of a first layer containing one or more drugs with immediate or controlled release formulation, a second layer containing one or more drugs, either equal to or different from the first layer, with slow release formulation, and a low-permeability barrier-type layer coating said second layer or, alternatively, placed between the first and second layer and, if necessary, containing a drug.		

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PHARMACEUTICAL TABLET CAPABLE OF LIBERATING ONE OR MORE DRUGS
AT DIFFERENT RELEASE RATES

PRIOR ART

5 The development of innovative pharmaceutical forms for drugs administration to humans and animals has lately been a source for considerable research effort in pharmaceutical technology.

One of the major innovations in this sector is the targeting of drugs release to a specific site of treatment and/or the release of said drug at a programmed rate.

10 The applications thereof are of consequence not only to human and animal health but also to agriculture.

Very many are the pharmaceutical forms already developed and disclosed in patents, which are capable of releasing the drug at zero-order kinetics.

15 As well known to those skilled in the pharmaceutical art, this means that the pharmaceutical form liberates the drug at a constant rate and over a scheduled period of time. In particular, drug release may occur according to the following empirical relation

$$M_t/M_\infty = Kt^n$$

20 where M_t/M_∞ is the fraction of released substance, K is a constant depending on the diffusion coefficient in the matrix and n is a constant depending on polymeric chains swelling and relaxation rate in swelling front.

Examples of said pharmaceutical forms are amply documented,

e.g. in "Novel drug delivery and its therapeutical application" by L.F. Prescott and W.S. Nimmo, J. Wiley, New York, 1989.

Examples refer to pharmaceutical forms that may be administered by different routes, i.e. oral, transdermic, vaginal, and ocular.

Obviously, due to the great importance and wide utilization of oral drug administration, many and diverse embodiments are for gastroenteric administration.

Among the widely known and used embodiments the OROS system, disclosed in USP 4,160,020 (1979), should be cited.

A further achievement in the area is the pharmaceutical form disclosed in USP 4,839,177 (1989) and in the subsequent Italian patent application No. 22694 dated 14th Dec., 1989. Said patents claim the preparation of pharmaceutical forms for oral administration capable of liberating a drug at a constant release rate, i.e. according to zero-order kinetics.

In particular, the aforesaid patents disclose and claim the preparation of a tablet which, in its simplest form, consists of a hydrophilic matrix containing a drug and suitable excipients allowing the sustained release of the drug.

The drug sustained release is brought about by gelable hydrophilic polymers, which swell by contact with water and/or aqueous fluids, giving a gelled layer wherefrom the drug is liberated according to Fick's type kinetics.

The pharmaceutical form claimed in the aforementioned patents is characterized by the matrix being partly coated with a

drug-impermeable barrier consisting of a polymeric film insoluble in water or in an aqueous medium. Alternatively, said barrier consists of polymeric mixtures or granular masses with technological adjuvants, applied by compression (Italian patent application No. 22694/89). The barrier obtained is drug-impermeable for at least 4-8 hrs and, therefore, hinders drug dispensing from the coated surface.

Therefore, the hydrophilic drug is exclusively released from the free area, generally at a constant rate.

However, the prior art does not envisage the possibility of obtaining products capable of releasing one or more drugs at different rates or else of releasing two different drugs sequentially, i.e. releasing the second drug only after releasing the first drug, both being contained in the same pharmaceutical form.

Several treatments require a sequential administration of two drugs and, therefore, involve complex posologic schemes and scrupulous patient's compliance therewith. Obviously, since such compliance is hardly obtainable, the above requirements can often be met only by hospitalized patients, carefully controlled by physicians and paramedical specialists.

As well known, complex therapeutic schemes are reluctantly accepted and scarcely followed by out-patients, the correct compliance with posologic schemes being inversely proportional to the treatment complexity and to the number of daily

administrations.

In particular very many are the conditions to be treated with sequentially acting drugs. For example, rheumatic night pain is to be treated with two drug doses, one on pain onset and the other at a later time, or with a pharmaceutical form slowly releasing the second dose so that a sufficiently high plasmatic level be maintained. In these cases, the pharmaceutical form should be capable of releasing the drug at the same rate as drug elimination.

As known, steroid and non-steroid anti-inflammatory agents can induce pyrosis and/or gastric mucosa irritation. A prior protection of the gastric mucosa by agents, such as sucralphate, aluminium glycinate, activated attapulgit or hydrotalcite, followed by the administration of the potentially gastrolesive drug, can increase the patients' tolerance for said drug.

Identical remarks can be made about the antibiotic posology, which usually are to be administered at sequential daily doses.

The same problems are also to be faced with drugs whose active ingredient is a metabolite thereof, the metabolism occurring at different rates in the various organs.

A typical example is L-dopa used in treating Parkinson's disease. In the organism, L-dopa is metabolized to dopamine, which is the drug active ingredient. However, only the unmodified form, i.e. L-dopa, is capable of crossing the blood-

brain barrier.

L-dopa is rapidly absorbed into the gastroenteric tract and spreads out in the various organs and tissues, including the CNS. L-dopa has plasmatic half-life of approx. 1 hr and is converted into dopamine mainly by decarboxylation.

L-dopa is rapidly decarboxylated to dopamine also in the gastroenteric tract: hence, the quantity of L-dopa reaching the CNS is extremely low. Furthermore, the presence of excess dopamine deriving from peripheral decarboxylation in organs external to the CNS may produce massive side effects.

Should drugs inhibiting peripheral decarboxylation, such as benserazide or carbidopa, be administered with or before L-dopa administration, the peripheral conversion of L-dopa into dopamine would be drastically reduced and higher amounts of L-dopa would reach the systemic circulation and the brain, where conversion into dopamine produces the desired therapeutic effect. Thus, much lower L-dopa doses can have a high therapeutic effect and, at the same time, produce lesser side effects.

In such complex pathological situations, the availability of pharmaceutical compositions capable of liberating different drugs at successive times would solve a therapeutic problem also involving a serious social impact, the treatments being mainly addressed to elderly persons.

SUMMARY

It has been found a new pharmaceutical tablet containing one or more drugs and liberating same at different release rates. This achievement solves the problems encountered so far.

5 Said tablet allows the administration of:

- a single drug, a portion thereof being released within a short time and the remaining portion being released over a longer period;

10 - two drugs or drug combinations, which are released at different rates.

The tablet as per the present invention consists of three layers, i.e.:

15 - a first layer containing one or more drugs with immediate or controlled release formulation, composed of rapidly swelling and/or soluble and/or erodible polymeric substances by contact with aqueous fluids, and adjuvants;

- a second layer containing one or more drugs, either equal to or different from those of the first layer, with slow release formulation, composed of swelling and/or gelable and/or
20 erodible polymeric substances by contact with aqueous fluids, and adjuvants;

- a low-permeability barrier-type layer coating said second layer or, alternatively, placed between the first and second layer, consisting of polymeric materials, adjuvants, plasticizing agents and, if necessary, a drug.
25

The tablet may be enteric coated.

Detailed description of the invention

The following detailed description sets forth the characteristics of and advantages offered by the claimed pharmaceutical tablets, which are capable of releasing one or more drugs at different rates.

Said tablet consists of:

- a first layer containing one or more drugs with immediate or controlled release formulation,
- a second layer containing one or more drugs, either equal to or different from those of the first layer, with slow release formulation, and
- a third layer, which is a low-permeability barrier coating said second layer or, alternatively, placed between said first and second layer and, if necessary, containing a drug. This layer serves the purpose of limiting the drug release surface of the adjacent layer or layers.

Preferred embodiments of the invention are shown in Figs. 1, 2, and 3.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig.1: 1 immediate or controlled release layer; 2 slow release layer; 3 barrier-type layer.

Fig. 2: 4 immediate or controlled release layer; 5 slow release layer; 6 barrier-type layer.

Fig. 3: 7 immediate or controlled release layer; 8 barrier-type layer; 9 slow release layer.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

An immediate or controlled release layer formulation consists of rapidly swelling and/or soluble and/or erodible polymeric substances by contact with aqueous fluids and convenient
5 adjuvants.

Said polymeric substances are selected from the group consisting of cross-linked polyvinylpyrrolidone, low- and medium-molecular-weight hydroxypropyl cellulose and hydroxypropyl methylcellulose, cross-linked sodium
10 carboxymethylcellulose, carboxymethyl starch, potassium methacrylate-divinylbenzene copolymer, polyvinyl alcohols, starches, starch derivatives, microcrystalline cellulose and cellulose derivatives, β -cyclodextrin and dextrin derivatives.

The amount of said polymeric substances in the layer is 1.0 to
15 90% by wt., preferably 20 to 70% by wt. Said adjuvants are selected from the categories of substances currently used in the typical pharmaceutical practice, such as diluents, buffers, adsorbents, etc., and in particular starch, pregelled starch, calcium phosphate, mannitol, lactose, saccharose, glucose,
20 sorbitol, microcrystalline cellulose, and binding agents, such as gelatin, polyvinylpyrrolidone, methylcellulose, starch solution, ethylcellulose, arabic gum, tragacanth gum.

Other excipients of typical pharmaceutical practice can be used as adjuvants, such as for example magnesium stearate, stearic
25 acid, colloidal silica, glyceryl monostearate, hydrogenated

castor oil, waxes, and mono-, bi-, and trisubstituted glycerides.

A slow release layer formulation consists of rapidly swelling and/or gelable and/or erodible polymeric substances by contact with aqueous fluids and convenient adjuvants.

Said polymeric substances are selected from the group consisting of hydroxypropyl methylcellulose having molecular weight from 1,000 to 4,000,000, hydroxypropyl cellulose having molecular weight from 2,000 to 2,000,000, carboxyvinyl polymers, polyvinyl alcohols, glucans, scleroglucans, mannans, xanthans, alginic acid and derivatives thereof, polymers and copolymers, such as poly(methyl vinyl ethers/maleic anhydride) carboxymethylcellulose and derivatives thereof, ethylcellulose, methylcellulose, and cellulose derivatives in general.

The amount of said polymeric substances, in respect of the layer total weight, is 5 to 90% by wt. and preferably 5 to 50% by wt.

Various types of all aforesaid polymers, characterized by different physico-chemical, solubility and gelling properties, are commercially available. In particular, various types of hydroxypropyl methylcellulose having different molecular weight (from 1,000 to 4,000,000) and different degree of substitution can be used. They show different characteristics because, depending on the degree of substitution of the polymeric chain, they are either prevailingly erodible or prevailingly gelable. Said adjuvants of the slow release layer are selected from the

same group as reported for the immediate or controlled release layer.

The barrier-type layer formulation consists of polymeric substances, adjuvants, and plasticizers.

- 5 The polymeric substances of the barrier-type layer are selected from the group consisting of hydroxypropyl methylcellulose having molecular weight from 1,000 to 4,000,000, hydroxypropyl cellulose having molecular weight from 2,000 to 2,000,000, carboxyvinyl polymers, polyvinyl alcohols, glucans, scleroglucans, mannans, xanthans, carboxymethylcellulose and derivatives thereof, ethylcellulose, methylcellulose, and cellulose derivatives in general. The amount of said polymeric substances, in respect of the layer total weight, is 5 to 90% by wt. and preferably 50 to 85% by wt.
- 10
- 15 Adjuvants are selected from the group consisting of glyceryl monostearate and semisynthetic triglyceride derivatives, semisynthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinylpyrrolidone, gelatin, ethylcellulose, methylcellulose, sodium carboxymethylcellulose, as well as other natural or synthetic substances well known to those skilled in the pharmaceutical art, i.e. magnesium stearate, stearic acid, sodium stearate, talc, sodium benzoate, boric acid, polyoxyethylene glycols, and colloidal silica.
- 20
- 25 As will be illustrated in more detail in the examples reported

hereinafter, also diluents, lubricants, buffers, antiblock and gliding agents, and other substances capable of bringing about the desired characteristics in said layer may be used, as described in the following examples.

- 5 Plasticizing agents are selected from the group consisting of hydrogenated castor oil, fatty acids, substituted triglycerides and glycerides, polyoxyethylene glycols and derivatives thereof having a different molecular weight generally ranging from 400 to 60,000. They serve the purpose of making the barrier-type layer as elastic as required.

The polymeric substances used, in combination with the other adjuvants, to prepare the barrier-type layer, make said layer impermeable to the drug of the adjacent layer for at least 4-6 hrs.

- 15 Several drugs may be present in the formulation of the three layers of the compressed tablet of the invention, e.g. anti-inflammatory steroids and non-steroid anti-inflammatory drugs (NSAID), such as diclofenac sodium, indomethacin, ibuprofen, ketoprofen, diflunisal, piroxicam, naproxen, flurbiprofen, tolmentin sodium; antibiotics such as ampicillin, amoxycillin, cephadrine, clavulanic acid, cephalor, cephalixin, cloxacillin, erythromycin, their salts and derivatives; urogenital antimicrobial agents, such as nitrofurantoin, nalidixic acid, oxolinic acid, pipemidic acid and its derivatives, sleep producing drugs and tranquilizers, such as
- 25 diazepam, nitrazepam, flurazepam, oxazepam, chlorthalidone,

medazepam, lorazepam; drugs for the prevention of anginal and hypertensive attacks, such as diltiazem, trapidil, urapidil, benziodarone, dipiridamole, lidoflazine, naphthhydrofuryl oxalate, perhexeline maleate, oxyfedrine hydrochloride; and
5 antihistaminics and/or antiasthmatics, such as ephedrine, terfenadine, theophylline, chlorpheniramine.

The compressed tablets of the invention can be prepared from granular mixtures according to current production techniques: therefore, their production on a commercial-scale can be
10 immediate.

For example, compressed tablets can be obtained by rotary presses operating at a pressure of 1000 to 5000 kg/cm².

The finished compressed tablets may be further coated with a polymeric film, which passes through the stomach unaltered and
15 is disintegrated in the intestine: the drug can be thus activated and released after reaching the intestinal tract.

The immediate release layer is 0.5 to 5.0 mm thick and has a drug content of 1 to 90% by wt.

The slow release layer is 0.5 to 5.0 mm thick and has a drug
20 content of 0.5 to 80% by wt.

The barrier-like layer is 0.1 to 4.5 mm thick and generally does not contain any drug. However, it may also contain a by wt. % amount of drug of 0.5 to 20.

As illustrated in the figures, the barrier-type layer may coat
25 one base of the compressed tablet or the side surface or the

side surface and one base.

The tablets, as per the invention, offer the advantage of releasing the drug or drugs according to a prefixed schedule; therefore lower amounts of drug - in respect of the traditional sustained release tablets - can be administered. Dose dumping is thus avoided and specific therapeutic requirements are met by active ingredients sequential liberation.

The tablets under the invention find very important therapeutic applications, e.g. when one or more drugs are to be administered at different times and when one drug must act immediately and another drug must be long-acting.

The following examples are conveyed by way of indication, not of limitation.

EXAMPLE 1

Compressed tablets as per Fig. 2 consisting of a layer 5 containing ephedrine hydrochloride (100 mg) with slow release formulation, a barrier-type layer 6, and a layer 4 containing further 100 mg ephedrine with immediate release formulation.

1 - a - Preparation of the granular mass for layer 5

	Ephedrine hydrochloride (B. 15910100, C. Erba)	100.0 mg
	Mannitol (C. Erba, Milan, I)	68.0 mg
	Hydroxypropyl methylcellulose (Methocel [®] K4 M,	
5	Colorcon, Orpington, UK)	20.0 mg
	Polyvinylpyrrolidone (Plasdone [®] K29-32, Gaf Corp.,	
	Wayne, NY, USA)	10.0 mg
	Magnesium stearate (C. Erba, Milan, I)	2.0 mg
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	1.0 mg

10	Total	201.0 mg

Ephedrine hydrochloride, mannitol, and hydroxypropyl methylcellulose were pounded in a mortar and wetted with a 20% ethanol solution of polyvinylpyrrolidone. The mixture was sieved through a 25 mesh sieve screen, oven dried to constant weight, sieved again through the same sieve screen, added with the lubricant and silica, and vortex mixed for 10 min.

The granular mass obtained A1, which exhibited good free flowing and compacting properties, was compressed as described hereinafter.

1 - b - Preparation of the granular mass for barrier-like layer
(6)

	Hydroxypropyl methylcellulose (Methocel [®] K100 M, Colorcon, Orpington, UK)	79.8%
5	Hydrogenated castor oil (Cutina HR, Henkel, Düsseldorf, D)	13.5%
	Ethylcellulose (Ethocel [®] 14 cP, BDH Chem. Ltd., Poole, UK)	5.0%
	20% FCF aluminium lake yellow EEC 110 (Colorcon, Orpington, UK)	0.5%
10	Magnesium stearate (USP grade, C. Erba, Milan, I)	1.0%
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	0.5%

Hydroxypropyl methylcellulose and hydrogenated castor oil were
pounded in a mortar, and the dyeing agent was accurately
15 dispersed. The mixture was wetted with a 5% ethanol solution of
ethylcellulose, sieved through a 25 mesh sieve screen, oven
dried at 30°C for 2 hrs approx., sieved again through a 25
mesh sieve screen, added with colloidal silica and Mg stearate,
and vortex mixed for 15 min.

20 The granular mass obtained B1, which exhibited good free
flowing and compacting properties, was compressed as described
hereinafter.

1 - c - Preparation of the granular mass for layer (4)

	Ephedrine hydrochloride (B. 15910100, C. Erba)	100.0 mg
	Lactose (C. Erba, Milan, I)	40.0 mg
	Starch from maize (C. Erba, Milan, I)	60.0 mg
5	Polyvinylpyrrolidone (Plasdone [®] K29-32, Gaf Corp., Wayne, NY, USA)	12.0 mg
	Carboxymethyl starch (Explotab [®] , Edward Mendell Co., Inc., Carmel, NY, USA)	10.0 mg
	Cross-linked polyvinylpyrrolidone (Polylasdone XL [®] , Gaf Corp., Wayne, NY, USA)	10.0 mg
10	Magnesium stearate (C. Erba, Milan, I)	2.0 mg
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	1.0 mg

Total		235.0 mg

15 Ephedrine, lactose, starch from maize were pounded in a mortar and wetted with a 20% ethanol solution of polyvinylpyrrolidone.

The mixture was sieved through a 25 mesh sieve screen, oven dried to constant weight, sieved again through the same sieve screen, added with carboxymethyl starch, cross-linked polyvinylpyrrolidone, magnesium stearate, and colloidal silica, and vortex mixed for 15 min.

20 The granular mass obtained C1, which exhibited good free flowing and compacting properties, was compressed as described

hereinafter.

1 - d - Preparation of compressed tablets

A Dry-Cota (Manesty, Liverpool, UK) rotary press was used for the manufacture of compressed tablets as illustrated in Fig. 2.

5 As well known to those skilled in the art, said press consists of two coupled rotary presses. The press used was equipped with circular concave punches (dia. 8.0 mm; R = 10.0 mm) for layer 5 formation and with circular concave punches (dia. 12.0 mm; R = 10.0 mm) for layers 4 and 6 formation.

10 In this Example and in the following ones, R stands for the punch bending radius.

The first press feed hopper was filled with granular mass A1 and the two second press feed hoppers were filled with granular mass B1 and C1, respectively. The first press was set to
15 produce 201 mg layers of granular mass A1 (equalling 100 mg of drug). The first hopper of the second press was set to deliver 230 mg of granular mass B1 while the second hopper was set to deliver 235 mg of granular mass C1 (equalling 100 mg of drug). The operating pressure was $\approx 2,000$ kg/cm². The compressed
20 tablets obtained averagely weighed 666 mg and contained 200 mg ephedrine hydrochloride.

The obtained tablets were subjected to the dissolution test described below.

1 - e - Dissolution test

25 The tablet release characteristics were evaluated by apparatus

1 (basket) disclosed in USP XXII, operated at 100 rpm. The dissolution fluid was deionized water (500 ml) at 37°C. Drug release was controlled by UV spectrophotometer set at 257 nm, using an automatic sampling and determination system and an
5 automatic programme for data processing (Spectracomp 602 of Advanced Products, Milan, Italy).

The results obtained are shown in Table 1.

Table 1

	Time (min)	released ephedrine (%)

10	10	42.1
	20	48.8
	30	52.0
	60	58.0
	120	65.6
15	240	75.9
	360	88.0
	480	95.8
	600	98.7
	720	99.9

20 The above data provide evidence that of the 200 mg of drug contained in the tablet, a portion was released within 20 to 30 min, and the remaining portion within 10 to 12 hrs.

EXAMPLE 2

Compressed tablets as per Fig. 2 consisting of a layer 5
25 containing ephedrine hydrochloride (100 mg) with slow release

formulation, a barrier-type layer 6, and a layer 4 containing 100 mg theophylline with controlled release formulation.

2 - a - Preparation of the granular mass for layer 5

	Ephedrine hydrochloride (B. 15910100, C. Erba)	100.0 mg
5	Mannitol (C. Erba, Milan, I)	68.0 mg
	Hydroxypropyl methylcellulose (Methocel [®] K4 M, Colorcon, Orpington, UK)	20.0 mg
	Polyvinylpyrrolidone (Plasdone [®] K29-32, Gaf Corp., Wayne, NY, USA)	10.0 mg
10	Magnesium stearate (C. Erba, Milan, I)	2.0 mg
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	1.0 mg

	Total	201.0 mg

Ephedrine hydrochloride, mannitol, and hydroxypropyl methylcellulose were pounded in a mortar and wetted with a 20% ethanol solution of polyvinylpyrrolidone. The mixture was sieved through a 25 mesh sieve screen, oven dried to constant weight, sieved again through the same sieve screen, added with the lubricant and silica, and vortex mixed for 10 min.

The granular mass obtained A2, which exhibited good free flowing and compacting properties, was compressed as described hereinafter.

2 - b - Preparation of the granular mass for barrier-like layer
(6)

	Hydroxypropyl methylcellulose (Methocel [®] K100 M, Colorcon, Orpington, UK)	79.8%
5	Hydrogenated castor oil (Cutina HR, Henkel, Düsseldorf, D)	13.5%
	Ethylcellulose (Ethocel [®] 14 cP, BDH Chem. Ltd., Poole, UK)	5.0%
	20% FCF aluminium lake yellow EEC 110 (Colorcon, Orpington, UK)	0.5%
10	Magnesium stearate (USP grade, C. Erba, Milan, I)	1.0%
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	0.5%

Hydroxypropyl methylcellulose and hydrogenated castor oil were
pounded in a mortar, and the dyeing agent was accurately
15 dispersed. The mixture was wetted with a 5% ethanol solution of
ethylcellulose, sieved through a 25 mesh sieve screen, oven
dried at 30°C for 2 hrs approx., sieved again through a 25
mesh sieve screen, added with colloidal silica and Mg stearate,
and vortex mixed for 15 min.

20 The granular mass obtained B2, which exhibited good free
flowing and compacting properties, was compressed as described
hereinafter.

2 - c - Preparation of the granular mass for layer 4

	Anhydrous theophylline (C. Erba, Milan, I)	100.0 mg
	Lactose (C. Erba, Milan, I)	50.0 mg
	Hydroxypropyl methylcellulose (Methocel [®] E5 Premium,	
5	Colorcon, Orpington, UK)	60.0 mg
	Polyvinylpyrrolidone (Plasdone [®] K29-32, Gaf Corp.,	
	Wayne, NY, USA)	12.0 mg
	Magnesium stearate (C. Erba, Milan, I)	2.0 mg
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	1.0 mg

10	Total	225.0 mg

Theophylline, lactose, hydroxypropyl methylcellulose were
pounded in a mortar and wetted with a 20% ethanol solution of
polyvinylpyrrolidone. The mixture was sieved through a 25 mesh
sieve screen, oven dried to constant weight, sieved again
15 through the same sieve screen, added with magnesium stearate
and colloidal silica, and vortex mixed for 15 min.

The C2 granular mass obtained, which exhibited good free
flowing and compacting properties, was compressed as described
hereinafter.

20 2 - d - Preparation of compressed tablets

A Dry-Cota (Manesty, Liverpool, UK) rotary press as described

in Example 1 was used for the manufacture of compressed tablets as illustrated in Fig. 2.

The first press feed hopper was filled with granular mass A2 and the two second press feed hoppers were filled with granular mass B2 and C2, respectively. The first press was set to produce 201 mg layers of granular mass A2, equalling 100 mg of drug (ephedrine). The first hopper of the second press was set to deliver 230 mg of granular mass B2 while the second hopper of the second press was set to deliver 225 mg granular mass C2, equalling 100 mg of drug (theophylline). The operating pressure was $\approx 2,000$ kg/cm². The compressed tablets obtained averagely weighed 656 mg and contained 100 mg ephedrine hydrochloride and 100 mg theophylline.

The obtained tablets were subjected to the dissolution test described below.

2 - e - Dissolution test

The tablet release characteristics of the two drugs were evaluated by apparatus 1 (basket) disclosed in USP XXII, operated at 100 rpm. The dissolution fluid was deionized water (1000 ml) at 37°C. Drug release was controlled by UV spectrophotometer set, respectively, at 257 nm for ephedrine and at 271 nm for theophylline, using an automatic sampling and determination system and an automatic programme for data processing (Spectracomp 602 of Advanced Products, Milan, Italy), or a chromatographic control method (HPLC).

The results obtained are shown in Table 2.

Table 2

	Time (min)	released theophylline (%)	released ephedrine (%)

	15	21.5	-
	30	47.0	-
5	60	84.1	-
	90	96.4	2.6
	120	100.8	10.3
	240	-	41.2
	360	-	66.5
10	480	-	85.8
	600	-	94.7
	720	-	99.9

The above data provide evidence that the drug release from layer 5 (ephedrine) occurred only after the drug controlled release from layer 4 (theophylline), which took 2 hrs approx.

EXAMPLE 3

Compressed tablets as per Fig. 2 consisting of a layer 5 containing ketoprofen (100 mg) with slow release formulation, a barrier-type layer 6, and a layer 4 containing further 100 mg ketoprofen with immediate release formulation.

3 - a - Preparation of the granular mass for layer (5)

	Ketoprofen (Soc.It.Med., Scandicci, Firenze, I)	100.0 mg
	Hydroxypropyl methylcellulose (Methocel [®] K4 M, Colorcon, Orpington, UK)	75.0 mg
5	Mannitol (C. Erba, Milan, I)	40.0 mg
	Polyvinylpyrrolidone (Plasdone [®] K29-32, Gaf Corp., Wayne, NY, USA)	14.5 mg
	Magnesium stearate (C. Erba, Milan, I)	1.0 mg
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	0.5 mg
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10	Total	231.0 mg

Ketoprofen, mannitol, and hydroxypropyl methylcellulose were
pounded in a mortar and wetted with a 20% ethanol solution of
polyvinylpyrrolidone. The mixture was sieved through a 25 mesh
sieve screen, oven dried to constant weight, sieved again
15 through the same sieve screen, added with magnesium stearate
and colloidal silica, and vortex mixed for 15 min.

The A3 granular mass obtained, which exhibited good free
flowing and compacting properties, was compressed as described
hereinafter.

25

3 - b - Preparation of the granular mass for barrier-like layer 6

	Hydroxypropyl methylcellulose (Methocel [®] K100 M, Colorcon, Orpington, UK)	79.8%
5	Hydrogenated castor oil (Cutina HR, Henkel, Düsseldorf, D)	13.5%
	Ethylcellulose (Ethocel [®] 14 cP, BDH Chem. Ltd., Poole, UK)	5.0%
	20% FCF aluminium lake yellow EEC 110 (Colorcon, Orpington, UK)	0.5%
10	Magnesium stearate (USP grade, C. Erba, Milan, I)	1.0%
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	0.5%

Hydroxypropyl methylcellulose and hydrogenated castor oil were pounded in a mortar, and the dyeing agent was accurately dispersed. The mixture was wetted with a 5% ethanol solution of ethylcellulose, sieved through a 25 mesh sieve screen, oven dried at 30°C for 2 hrs approx., sieved again through a 25 mesh sieve screen, added with sieved colloidal silica and Mg stearate, and vortex mixed for 15 min.

20 The B3 granular mass obtained, which exhibited good free flowing and compacting properties, was compressed as described hereinafter.

3 - c - Preparation of the granular mass for layer 4

	Ketoprofen (Soc.It.Med., Scandicci, Firenze, I)	100.0 mg
	Starch from maize (C. Erba, Milan, I)	80.0 mg
	Methylcellulose (500-600 cps BDH Chemicals Ltd.,	
5	Poole, UK)	1.0 mg
	Carboxymethyl starch (Explotab [®] , Edward Mendell	
	Co. Inc., Carmel, NY, USA)	19.5 mg
	Cross-linked polyvinylpyrrolidone (Polylasdone XL [®] ,	
	Gaf Corp., Wayne, NY, USA)	20.0 mg
10	Magnesium stearate (C. Erba, Milan, I)	1.0 mg
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	0.5 mg
	Total	222.0 mg

Ketoprofen and starch from maize were pounded in a mortar and wetted with a 1% methylcellulose aqueous solution. The mixture

15 was sieved through a 25 mesh sieve screen, oven dried to constant weight, and sieved again through the same sieve screen, added with carboxymethyl starch, cross-linked polyvinylpyrrolidone, magnesium stearate, and colloidal silica, and vortex mixed for 15 min.

20 The C3 granular mass obtained, which exhibited good free flowing and compacting properties, was compressed as described hereinafter.

3 - d - Preparation of compressed tablets

A Dry-Cota (Manesty, Liverpool, UK) rotary press as described in Example 1 was used for the manufacture of compressed tablets as illustrated in Fig. 2. The first press feed hopper was
5 filled with the granular mass described under 3-a granular mass A3 and the two second press feed hoppers were filled with the granular masses described under 3-b B3 and 3-c C3, respectively. The first press was set to produce 231 mg layers of granular mass A3, equalling 100 mg of drug (ketoprofen).
10 The first hopper of the second press was set to deliver 230 mg of granular mass B3 while the second hopper of the second press was set to deliver 222 mg of granular mass C3 (equalling 100 mg of drug). The operating pressure was $\approx 2,000$ kg/cm². The compressed tablets obtained averagely weighed 683 mg and
15 contained 200 mg ketoprofen.

The obtained tablets were subjected to the dissolution test described below.

3 - e - Dissolution test

The tablet release characteristics were evaluated by apparatus
20 1 (basket) disclosed in USP XXII, operated at 100 rpm. The dissolution fluid was simulated intestinal fluid (USP XXII) (1000 ml) without enzymes at 37°C. Drug release was controlled by UV spectrophotometer set at 264 nm, using an automatic sampling and determination system and an automatic programme
25 for data processing (Spectracomp 602 of Advanced Products, Milan, Italy).

The results obtained are shown in Table 3.

Table 3

	Time (hrs)	released ketoprofen (%)

	0.5	48.2
5	1	49.2
	2	50.2
	4	53.2
	6	58.3
	8	62.1
10	10	69.8
	14	78.6
	18	89.3
	24	99.6

The above data provide evidence that 50% of drug was released within 30 min and the remaining 50% within 24 hrs approx.

EXAMPLE 4

Compressed tablets having the characteristics shown in per Fig. 1 consisting of a layer 1 containing the drug (ephedrine hydrochloride) with immediate release formulation, a layer 2 containing the same drug with slow release formulation, and a barrier-type layer 3 limiting the drug release from the layers underneath.

For tablet preparation, three different granular mass types were used, having respectively the following characteristics:

4 - a - Granular mass for layer 1

	Ephedrine hydrochloride (B. 15910100, C. Erba)	100.0 mg
	Lactose (C. Erba, Milan, I)	40.0 mg
	Starch from maize (C. Erba, Milan, I)	60.0 mg
5	Polyvinylpyrrolidone (Plasdone [®] D29-32, Gaf Corp., Wayne, NY, USA)	12.0 mg
	Carboxymethyl starch (Explotab [®] , Edward Mendell Co. Inc., Carmel, NY, USA)	10.0 mg
	Cross-linked polyvinylpyrrolidone (Polylasdone XL [®] , 10 Gaf Corp., Wayne, NY, USA)	10.0 mg
	Magnesium stearate (C. Erba, Milan, I)	2.0 mg
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	1.0 mg
		<hr/>
Total		235.0 mg

15 Ephedrine, lactose, and starch from maize were pounded in a
mortar and wetted with a 20% ethanol solution of
polyvinylpyrrolidone. The mixture was sieved through a 25 mesh
sieve screen, oven dried to constant weight, sieved again
through the same sieve screen, added with carboxymethyl starch,
cross-linked polyvinylpyrrolidone, magnesium stearate, and
20 colloidal silica, and vortex mixed for 15 min.

The granular mass obtained A⁴, which exhibited good free
flowing and compacting properties, was compressed as described

hereinafter.

4 - b - Granular mass for layer 2

	Ephedrine hydrochloride (B.15910100, C. Erba)	100.0 mg
	Mannitol (C. Erba, Milan, I)	68.0 mg
5	Hydroxypropyl methylcellulose (Methocel [®] K4 M, Colorcon, Orpington, UK)	20.0 mg
	Polyvinylpyrrolidone (Plasdone [®] K29-32, Gaf Corp., Wayne, NY, USA)	10.0 mg
	Magnesium stearate (C. Erba, Milan, I)	2.0 mg
10	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	1.0 mg

| | Total | 201.0 mg |

Ephedrine hydrochloride, mannitol, and hydroxypropyl methylcellulose were pounded in a mortar, wetted with a 20% ethanol solution of vinylpyrrolidone, sieved through a 25 mesh sieve screen, oven dried to constant weight, sieved again through the same sieve screen, added with the lubricant and silica, and vortex mixed for 10 min.

The granular mass obtained C4, which exhibited good free flowing and compacting properties, was compressed as described hereinafter.

4 - c - Granular mass for barrier-like layer 3

	Hydroxypropyl methylcellulose (Methocel [®] K100 M, Colorcon, Orpington, UK)	79.8%
5	Hydrogenated castor oil (Cutina HR, Henkel, Düsseldorf, D)	13.5%
	Ethylcellulose (Ethocel [®] 14 cP, BDH Chem. Ltd., Poole, UK)	5.0%
	20% FCF aluminium lake yellow EEC 110 (Colorcon, Orpington, UK)	0.5%
10	Magnesium stearate (USP grade, C. Erba, Milan, I)	1.0%
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	0.5%

Hydroxypropyl methylcellulose and hydrogenated castor oil were
pounded in a mortar, and the dyeing agent was accurately
dispersed. The mixture was wetted with a 5% ethanol solution of
15 ethylcellulose, sieved through a 25 mesh sieve screen, oven
dried at 30°C for 2 hrs approx., sieved again through a 25
mesh sieve screen, added with colloidal silica and Mg stearate,
and vortex mixed for 15 min.

The granular mass obtained B4, which exhibited good free
20 flowing and compacting properties, was compressed as described
hereinafter.

The three granular masses obtained as described above were
loaded into the three feed hoppers of a rotary press fit for

producing three-layer tablets, equipped with circular flat punches 10 mm in diameter (Layer-press, Manesty, Liverpool, UK). The press was set to feed the first loading station with 235 mg of granular mass A⁴, equalling 100 mg of drug, the
5 second loading station with 201 mg of granular mass C⁴, equalling 100 mg of drug, and the third loading station with 60 mg of granular mass B⁴. Said amount of B⁴ proved to be sufficient to produce a polymeric layer drug-impermeable for over 4 to 6 hrs.

10 Therefore, the press automatically produces a three-layer tablet, the first layer releasing 100 mg ephedrine within a short time and the second layer releasing 100 mg ephedrine within a longer time.

The preparation was controlled by dissolution tests carried out
15 with the equipment (basket, 100 rpm) and according to the method disclosed in USP XXII. The dissolution fluid was distilled water at 37°C.

Table 4

	Time (min)	released ephedrine hydrochloride (mg)
	0	0
	5	100
5	15	125
	30	130
	60	145
	120	170
	180	180
10	360	200

The above data provide evidence that the tablet can release a first portion (100 mg) immediately and the remaining portion (100 mg) gradually. For the purpose of comparison and of evaluating the efficiency of layer 3, a compressed tablet without said layer and, therefore, consisting only of layers 1 and 2 was also prepared.

Dissolution test carried out according to the procedure described above gave the following results.

Table 4a

Time (min)	released ephedrine hydrochloride (mg)
------------	---------------------------------------

0	0
5	100
15	140
30	155
60	180
120	195
150	200

5 A comparison between these data and those previously reported shows that the release of the second drug portion from the compressed tablet was considerably slowed down by the barrier-type layer.

15 To provide a further evidence, a compressed tablet with barrier-type layer 8 between immediate release layer 7 and slow release layer 9 was prepared (Fig. 3). The drug release of the tablet thus obtained was comparable with that referred to in Table 1, which gives a further proof of the drug release from the tablet being slowed down by the barrier-type layer.

20 EXAMPLE 5

Compressed tablets as shown in Fig. 2 consisting of a layer 5 containing ketoprofen (100 mg) with low release formulation, a barrier-type layer 6, and a layer 4 containing 200 mg sucralphate with immediate release formulation.

a- Preparation of the granular mass for layer 5

	Ketoprofen (Soc.It.Med., Scandicci, Firenze, I)	100.0 mg
	Hydroxypropyl methylcellulose (Methocel [®] K4 M, Colorcon, Orpington, UK)	75.0 mg
5	Mannitol (C. Erba, Milan, I)	40.0 mg
	Polyvinylpyrrolidone (Plasdone [®] K29-32, Gaf Corp., Wayne, NY, USA)	14.5 mg
	Magnesium stearate (C. Erba, Milan, I)	1.0 mg
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	0.5 mg
		<hr/>
10	Total	231.0 mg

Ketoprofen, mannitol, and hydroxypropyl cellulose were pounded in a mortar and wetted with a 20% ethanol solution of polyvinylpyrrolidone. The mixture was sieved through a 25 mesh sieve screen, oven dried to constant weight, sieved again through the same sieve screen, added with magnesium stearate and colloidal silica, and vortex mixed for 15 min.

The granular mass obtained A5, which exhibited good free flowing and compacting properties, was compressed as described hereinafter.

5 - b - Preparation of the granular mass for barrier-like layer 6

	Hydroxypropyl methylcellulose (Methocel [®] E5, Colorcon, Orpington, UK)	79.8%
5	Hydrogenated castor oil (Cutina HR, Henkel, Düsseldorf, D)	13.5%
	Ethylcellulose (Ethocel [®] 14 cP, BDH Chem. Ltd., Poole, UK)	5.0%
	20% FCF aluminium lake yellow EEC 110 (Colorcon, Orpington, UK)	0.5%
10	Magnesium stearate (USP grade, C. Erba, Milan, I)	1.0%
	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	0.5%

- Hydroxypropyl methylcellulose and hydrogenated castor oil were pounded in a mortar, and the dyeing agent was accurately dispersed. The mixture was wetted with a 5% ethanol solution of ethylcellulose, sieved through a 25 mesh sieve screen, oven dried at 30°C for 2 hrs approx., sieved again through a 25 mesh sieve screen, added with colloidal silica and Mg stearate, and vortex mixed for 15 min.
- 20 The granular mass obtained B5, which exhibited good free flowing and compacting properties, was compressed as described hereinafter.

5 - c - Preparation of the granular mass for layer 4

	Sucralphate	200.0 mg
	Starch from maize (C. Erba, Milan, I)	100.0 mg
	Polyvinylpyrrolidone (Plasdone® K29-32, Gaf Corp.,	
5	Wayne, NY, USA)	15.0 mg
	Carboxymethyl starch (Explotab®, Edward Mendell	
	Co. Inc., Carmel, NY, USA)	25.0 mg
	Talc (C. Erba, Milan, I)	4.0 mg
	Magnesium stearate (C. Erba, Milan, I)	2.0 mg
		<hr/>
10	Total	346.0 mg

Sucralphate and starch from maize were pounded in a mortar and wetted with a 20% alcohol solution of polyvinylpyrrolidone. The mixture was sieved through a 25 mesh sieve screen, oven dried to constant weight, sieved again through the same sieve screen,

15 added with carboxymethyl starch, talc, and magnesium stearate, and vortex mixed for 15 min.

The granular mass obtained C5, which exhibited good free flowing and compacting properties, was compressed as described hereinafter.

20 5 - d - Preparation of finished systems (by compression)

A Dry-Cota (Manesty, Liverpool, UK) rotary press as described in Example 1 was used for the manufacture of compressed tablets

as illustrated in Fig. 2. The first press feed hopper was filled with granular mass A5 and the two second press feed hoppers were filled with granular mass B5 and C5, respectively. The first press was set to produce 231 mg layers (equalling 100 mg of drug). The first hopper of the second press was set to deliver 230 mg of granular mass B5 and the second hopper of the second press was set to deliver 346 mg of granular mass C5 (equalling 200 mg of drug). The operating pressure was \approx 2,000 kg/cm².

The compressed tablets obtained averagely weighed 807 mg and contained 100 mg ketoprofen and 200 mg sucralphate. The obtained tablets were subjected to the dissolution test described below.

5 - e - Disintegration and dissolution test

The tablet release characteristics of the two drugs were evaluated. The time of disintegration of the layer containing sucralphate was determined by an ad-hoc apparatus according to USP. Ketoprofen dissolution test was carried out with apparatus 1 (basket, 100 rpm) described in USP XXII, in 1000 ml simulated intestinal fluid (USP XXII) without enzymes at 37°C. Drug (ketoprofen) release was controlled by UV spectrophotometer set at 264 nm, using an automatic sampling and determination system and an automatic programme for data processing (Spectracomp 602 of Advanced Products, Milan, Italy).

As far as ketoprofen is concerned, the results obtained are shown in Table 5.

Table 5

Time of disintegration of the layer containing sucralphate: 5 min.

Ketoprofen dissolution test:

	Time (h)	released ketoprofen (%)
	1	2.5
	2	4.7
10	4	10.5
	6	21.7
	8	34.6
	10	46.6
	14	64.5
15	18	88.9
	24	100.1

The results provide evidence that ketoprofen was released in 24 hrs approx.

The amount of sucralphate released was determined according to the method described in Pharmacopoeial Forum, May-June 1992, p. 3389: the results obtained proved that sucralphate was fast released.

EXAMPLE 6

Compressed tablets as shown in Fig. 1 consisting of a layer 1 containing amoxycillin trihydrate with immediate release

formulation, a layer 2 containing the same drug as layer 1 with slow release formulation, and a barrier-type layer 3 serving the purpose of slowing down drug release from the layer underneath.

5 Three different granular mass types having the following characteristics were used:

6 - a - Mixture for the preparation of layer 1

	Amoxycillin trihydrate (equalling 250 mg amoxycillin)	
	(Ribon, Milan, I)	287.0 mg
10	Microcrystalline cellulose (Avicel PH 102)	100.0 mg
	Carboxymethyl starch (Explotab [®] , Edward Mendell	
	Co. Inc., Carmel, NY, USA)	20.0 mg
	Talc (C. Erba, Milan, I)	40.0 mg
	Magnesium stearate (C. Erba, Milan, I)	15.0 mg
15	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	10.0 mg

	Total	452.0 mg

Amoxycillin trihydrate, microcrystalline cellulose, carboxymethyl starch, talc, magnesium stearate, and colloidal silica were vortex mixed for 15 min. The mixture obtained

20 A6, which exhibited good free flowing and good compacting by direct compression, was compressed as described hereinafter.

6 - b - Granular mass for layer 2 preparation

	Amoxycillin trihydrate (equalling 250 mg amoxycillin)	
	(Ribon, Milan, I)	287.0 mg
	Hydroxypropyl methylcellulose (Methocel [®] K15 M,	
5	Colorcon, Orpington, UK)	100.0 mg
	Mannitol (C. Erba, Milan, I)	50.0 mg
	Polyvinylpyrrolidone (Plasdone [®] K29-32, Gaf Corp.,	
	Wayne, NY, USA)	20.0 mg
	Talc (C. Erba, Milan, I)	5.0 mg
10	Magnesium stearate (C. Erba, Milan, I)	2.0 mg
	Total	464.0 mg

Amoxycillin trihydrate, mannitol, and hydroxypropyl methylcellulose were pounded in a mortar, was wetted with a 10% ethanol solution of polyvinylpyrrolidone, sieved through a 25 mesh sieve screen, oven dried to constant weight, sieved again through the same sieve screen, added with Mg stearate and talc, and vortex mixed for 15 min.

The granular mass obtained C6, which exhibited good free flowing and compacting properties, was compressed as described hereinafter.

6 - c - Granular mass for barrier-type layer 3

	Hydroxypropyl methylcellulose (Methocel [®] K100 M, Colorcon, Orpington, UK)	74.6%
5	Hydrogenated castor oil (Cutina HR, Henkel, Düsseldorf, D)	15.4%
	Ethylcellulose (Ethocel [®] 14 cP, BDH Chem. Ltd., Poole, UK)	8.0%
	FCF blue EEC 133 (Colorcon, Orpington, UK)	0.5%
	Magnesium stearate (USP grade, C. Erba, Milan, I)	1.0%
10	Colloidal silica (Syloid 244, Grace GmbH, Worms, D)	0.5%

Hydroxypropyl methylcellulose and hydrogenated castor oil were
pounded in a mortar, and the dyeing agent was accurately
dispersed. The mixture was wetted with a 5% ethanol solution of
ethylcellulose, sieved through a 25 mesh sieve screen, oven
15 dried at 30°C for 2 hrs approx., sieved again through a 25
mesh sieve screen, added with sieved colloidal silica and Mg
stearate, and vortex mixed for 15 min.

The granular mass obtained B6, which exhibited good free
flowing and compacting properties, was compressed as described
20 hereinafter.

The three granular masses obtained as described above were
loaded into three feed hoppers of a rotary press capable of
producing three-layer tablets, equipped with oval concave

punches (9.0 x 19.0 mm; R = 10.0 mm) (Layer-press, Manesty, Liverpool, UK).

The press was set to feed the first loading station with 452 mg of mixture A6, equalling 250 mg of drug, the second loading
5 station with 464 mg of granular mass C6, equalling 250 mg of drug, and the third loading station with 112 mg of granular mass B6. Said amount of B6 proved to be sufficient to produce a polymeric layer drug-impermeable for over 4 to 6 hrs.

Therefore, the press can automatically produce a pharmaceutical
10 form consisting of a three-layer compressed tablet, the first layer releasing 250 mg amoxycillin within a short time and the second layer releasing 250 mg amoxycillin within a longer time. The preparation was controlled by dissolution tests carried out with the equipment (basket, 100 rpm) and according to the
15 method disclosed in USP XXII. The dissolution fluid was 0.1N HCl (1000 ml) at 37°C. Drug release was controlled by UV spectrophotometer set at 230 nm, using an automatic sampling and determination system and an automatic programme for data processing (Spectracomp 602 of Advanced Products, Milan,
20 Italy).

The results obtained are shown in Table 6.

Table 6

	Time (min)	released amoxycillin (%)

	5	55.2
	30	62.1
5	60	66.2
	120	71.4
	240	79.2
	360	85.7
	480	91.5
10	720	100.1

In this case, the first drug portion was released immediately (in 5 min) and the second portion in 12 hrs approx.

CLAIMS

- 1 1. Pharmaceutical compressed tablet capable of releasing one or
2 more drugs at different rates, consisting of three layers,
3 wherein
4 - a first layer contains one or more drugs with immediate or
5 controlled release formulation, composed of rapidly swelling
6 and/or soluble and/or erodible polymeric substances by contact
7 with aqueous fluids, and adjuvants;
8 - a second layer contains one or more drugs, either equal to or
9 different from those of the first layer, with slow release
10 formulation, composed of swelling and/or gelable and/or
11 erodible polymeric substances by contact with aqueous fluids,
12 and adjuvants;
13 - a low-permeability barrier-type layer coating said second
14 layer or, alternatively, placed between the first and second
15 layer, consisting of polymeric substances, adjuvants,
16 plasticizing agents and, if necessary, a drug.
- 1 2. The compressed tablet according to claim 1, wherein said
2 polymeric substances of said first layer are selected from the
3 group consisting of cross-linked polyvinylpyrrolidone, low- and
4 medium-molecular-weight hydroxypropyl cellulose and
5 hydroxypropyl methylcellulose, cross-linked sodium
6 carboxymethylcellulose, carboxymethyl starch, potassium
7 methacrylate-divinylbenzene copolymer, polyvinyl alcohols,
8 starches, starch derivatives, microcrystalline cellulose and

9 cellulose derivatives, β -cyclodextrin and dextrin derivatives.

1 3. The compressed tablet according to claim 1, wherein said
2 polymeric substances of said first layer equal 1.0 to 90% by
3 wt. of said layer.

1 4. The compressed tablet according to claim 1, wherein said
2 adjuvants of said first layer are selected from the group
3 consisting of starch, pregelled starch, calcium phosphate,
4 mannitol, lactose, saccharose, glucose, sorbitol,
5 microcrystalline cellulose, gelatin, polyvinylpyrrolidone,
6 methylcellulose, starch solution, ethylcellulose, arabic gum,
7 tragacanth gum, magnesium stearate, stearic acid, colloidal
8 silica, glyceryl monostearate, hydrogenated castor oil, waxes,
9 and mono-, bi-, and trisubstituted glycerides.

1 5. The compressed tablet according to claim 1, wherein said
2 polymeric substances of said second layer are selected from the
3 group consisting of hydroxypropyl methylcellulose having
4 molecular weight from 1,000 to 4,000,000, hydroxypropyl
5 cellulose having molecular weight from 2,000 to 2,000,000,
6 carboxyvinyl polymers, polyvinyl alcohols, glucans,
7 scleroglucans, mannans, xanthans, alginic acid and derivatives
8 thereof, carboxymethylcellulose and derivatives thereof,
9 poly(methyl vinyl ethers/maleic anhydride), ethylcellulose,
10 methylcellulose, and cellulose derivatives.

1 6. The compressed tablet according to claim 1, wherein said
2 polymeric substances of said second layer equal 5 to 90% by wt.
3 of said layer.

1 7. The compressed tablet according to claim 1, wherein said
2 adjuvants of said second layer are selected from the same group
3 as the adjuvants of said first layer.

1 8. The compressed tablet according to claim 1, wherein said
2 polymeric substances of said barrier-type layer are selected
3 from the group consisting of hydroxypropyl methylcellulose
4 having molecular weight from 1,000 to 4,000,000, hydroxypropyl
5 cellulose having molecular weight from 2,000 to 2,000,000,
6 carboxyvinyl polymers, polyvinyl alcohols, glucans,
7 scleroglucans, mannans, xanthans, carboxymethylcellulose,
8 ethylcellulose, and methylcellulose.

1 9. The compressed tablet according to claim 1, wherein said
2 polymeric substances of said barrier-type layer equal 5 to 90%
3 by wt. of said layer.

1 10. The compressed tablet according to claim 1, wherein said
2 adjuvants of said barrier-type layer are selected from the
3 group consisting of glyceryl monostearate, semisynthetic
4 glycerides, glyceryl palmitostearate, glyceryl behenate,
5 polyvinylpyrrolidone, gelatin, ethylcellulose, methylcellulose,
6 sodium carboxymethylcellulose, magnesium stearate, stearic
7 acid, sodium stearate, talc, sodium benzoate, boric acid, and
8 colloidal silica.

1 11. The compressed tablet according to claim 1, wherein said
2 plasticizing agents of said barrier-type layer are selected
3 from the group consisting of hydrogenated castor oil, fatty

4 acids, substituted triglycerides and glycerides,
5 polyoxyethylene glycols and derivatives thereof having
6 molecular weight from 400 to 60,000.

1 12. The compressed tablet according to claim 1, wherein said
2 drugs are selected from the group consisting of diclofenac
3 sodium, indomethacin, ibuprofen, ketoprofen, diflunisal,
4 piroxicam, naproxen, flurbiprofen, tolmentin sodium,
5 ampicillin, amoxycillin, cephradine, clavulanic acid,
6 cephachlor, cephalexin, cloxacillin, erythromycin, their salts
7 and derivatives, nitrofurantoin, nalidixic acid, oxolinic
8 acid, pipemidic acid and its derivatives, diazepam,
9 nitrazepam, flurazepam, oxazepam, chlordiazepoxide, medazepam,
10 lorazepam, diltiazem, trapidil, urapidil, benziodarone,
11 dipiridamole, lidoflazine, naphthhydrofuryl oxalate, perhexeline
12 maleate, oxyfedrine hydrochloride, ephedrine, terfenadine,
13 theophylline, and chlorpheniramine.

1 13. The compressed tablet according to claim 1, wherein said
2 first layer is 0.5 to 5 mm thick and contains 1 to 90% by wt.
3 of drug.

1 14. The compressed tablet according to claim 1, wherein said
2 second layer is 0.5 to 5 mm thick and contains 0.5 to 80% by
3 wt. of drug.

1 15. The compressed tablet according to claim 1, wherein said
2 barrier-type layer is 0.1 to 4.5 mm thick and contains 0 to 20%
3 by wt. of drug.

1/1

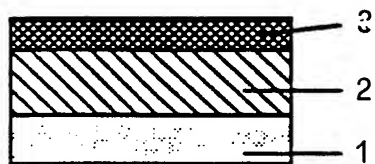


FIG. 1

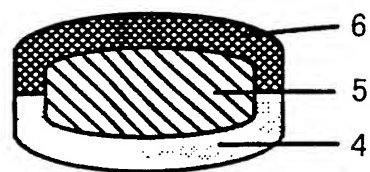


FIG. 2

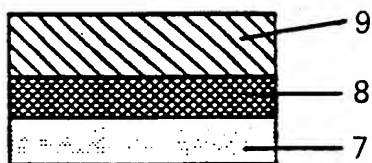


FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 93/02556

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 432 607 (JAGOTEC AG) 19 June 1991 cited in the application see the whole document ---	1-15
A	EP,A,0 226 884 (COLOMBO ET AL.) 1 July 1987 see page 9, line 21 - page 10, line 7 & US,A,4 839 177 (COLOMBO ET AL.) cited in the application ---	1-15
Y	GB,A,2 203 338 (ALZA CORPORATION) 19 October 1988 see the whole document ---	1-3,5-15
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

20 January 1994

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

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A	WO,A,91 04015 (BUKH MEDITEC) 4 April 1991 see page 31, line 34 - page 32, line 30 see figures 3,4,9 see page 46 - page 49; example 7 ---	1
A	GB,A,1 022 171 (THE WELLCOME FOUNDATION) 9 March 1966 -----	

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Information on patent family members

International Application No

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